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(19) (CA) # CANADIAN PATENT

(54) TETRACYCLIC ANTIINFLAMMATORY AGENTS

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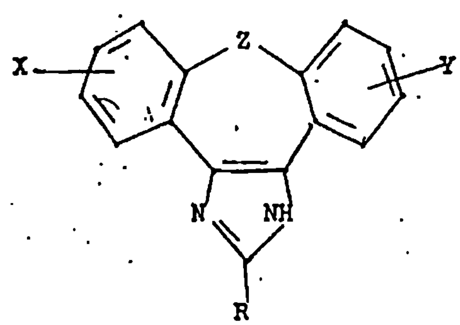
This invention relates to tetracyclic imidazoles, and more particularly to a series of 2-substituted dibenzo-[b,f]thiepin[4,5-d]- and dibenzo[3,4,7,8]cycloöcta[1,2-d]-imidazoles and their pharmaceutically acceptable acid addition salts as a novel class of antiinflammatory agents. Synthesis of these compounds is achieved through a condensation of the requisite α-diketone, and aldehyde and ammonium acetate.

References directed toward polycyclicimidazoles are not common in the chemical literature; Steck and Day, J. Am. Chem. Soc., 65, 452 (1943), in an effort to determine the course of the reaction involved in imidazole formation synthesized a series of phenanthrimidazoles. No utility, however, was disclosed for these compounds.

The tetracyclic antiinflammatory agents of this invention are represented by the formula:



and the pharmaceutically acceptable acid addition salts thereof, where:

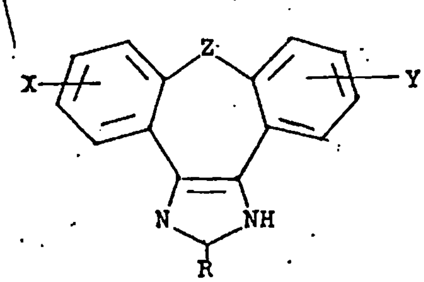
A is $-CH_2CH_2-$ or S;

X and Y are each hydrogen, methyl, methoxy, fluorine, chlorine, bromine or methylthio; and

R is trifluoromethyl, pyridyl, naphthyl or phenyl or substituted phenyl where the substituent is methyl, methoxy, fluorine, chlorine, bromine, dimethylamino, carboxy or methylthio.

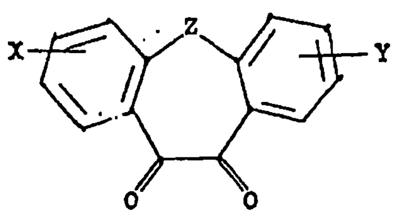
Of particular interest are congeners wherein Z is ethylene, X and Y are hydrogen and R is phenyl, 3-pyridyl or trifluoromethyl, and those wherein Z is sulphur, X and Y are hydrogen and R is p-methoxyphenyl, 3-pyridyl, trifluoromethyl or p-carboxyphenyl.

In accordance with the process for preparing the tetracyclicimidazoles of the present invention of formula I:



I

wherein Z, X, Y and R are as previously indicated, the following scheme is illustrative:

 + RCHO + $CH_3CO_2NH_4$ —— I

The above illustrated reaction is conducted under reaction conditions which are essentially those as employed by Davidson, et al., J. Org. Chem., 2, 319 (1937), and comprises heating a mixture of an α-diketone, an aldehyde or derivative thereof and ammonium acetate in a solvent of glacial acetic acid. As much as five to ten fold excess of ammonium acetate can be employed. The amount of aldehyde used in relation to the diketone can vary from an equimolar amount to as much as a 100% excess.

In general, reflux temperatures are considered desirable although lower temperatures with correspondingly longer reaction periods are operable. When said reflux temperatures are employed reaction times of 1-12 hours are adequate to yield the desired product.

A convenient method for isolation of the product comprises dilution of the reaction mixture with water followed by neutralization with ammonium hydroxide to a pH of approximately 7. The resulting precipitate is then filtered, dried and recrystallized from an appropriate solvent.

The requisite α-diketones wherein X and Y are as defined and Z is ethylene are synthesized according to the method taught by Leonard, et al., J. Am. Chem. Soc., 77, 5078 (1955). Further, α-diketones wherein X and Y are as indicated and Z is sulphur are prepared by selenium dioxide oxidation of the corresponding monoketones which, in turn,

are made according to the procedure as taught by Jilek, et al., Monatsh. Chem., 96, 201 (1965). The appropriate aldehydes are either commercially available or easily prepared by one skilled in the art according to the methods as outlined by Carnduff, Quart. Rev., 20, 169 (1966).

A characteristic of the compounds of the present invention is the acidic nature of the imidazole hydrogen and the property to form salts with basic reagents such as alkali metal hydroxides, alkoxides or hydrides and alkali earth metal hydroxides.

As has been previously mentioned, the compounds of the present invention, in addition to forming salts with basic reagents, can also, as previously mentioned form acid addition salts. Said compounds of the present invention are converted to the acid addition salts by interaction of the base with an acid either in an aqueous or nonaqueous medium. In a similar manner, treatment of the acid addition salts with an equivalent amount of an aqueous base solution, e.g., alkali metal hydroxides, alkali metal carbonates and alkali metal bicarbonates or with an equivalent amount of a metal cation which forms an insoluble precipitate with the acid anion, results in a regeneration of the free base form. Such conversions are best carried out as rapidly as possible and under temperature conditions and method dictated by the stability of said basic products. The bases thus regenerated may be reconverted to the same or a different acid addition salt.

In the utilization of the chemotherapeutic activity of those compounds of the present invention which form salts, it is preferred, of course, to use pharmaceutically

acceptable salts. Although water-insolubility, high toxicity, or lack of crystalline nature may make some particular salt species unsuitable or less desirable for use as such in a given pharmaceutical application, the water insoluble or toxic salts can be converted to the corresponding pharmaceutically acceptable bases by decomposition of the salt as described above, or alternately they can be converted to any desired pharmaceutically acceptable acid addition salt.

Examples of acids which provide pharmaceutically acceptable anions are hydrochloric, hydrobromic, hydroiodic, nitric, sulfuric, or sulfurous, phosphoric, acetic, lactic, citric, tartaric, succinic, maleic, and gluconic acids.

As previously indicated, the tetracyclicimidazoles of the present invention are all readily adapted to therapeutic use as antiinflammatory agents in mammals. Outstanding for their effectiveness in this regard are the following agents: 8,9-dihydro-2-phenyldibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole (I: $Z = CH_2CH_2$-; X, Y = H and R = ϕ), 8,9-dihydro-2-(3-pyridyl)-dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole (I: Z = $-CH_2CH_2$-; X, Y = H and R = 3-pyridyl), 8,9-dihydro-2-trifluoromethyldibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole (I: Z = $-CH_2CH_2$-; X, Y = H and R = CF_3), 2-trifluoromethyldibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = CF_3), 2-(p-methoxyphenyl)dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = p-$CH_3OC_6H_4$), 2-(3-pyridyl)dibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = 3-pyridyl) and 2-(p-carboxyphenyl)dibenzo-[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = H and R = p-$HO_2CC_6H_4$).

A standard procedure for detecting and comparing

antiinflammatory activity of compounds in this series and for which there is an excellent correlation with human efficacy is the carrageenin rat foot edema test of Winter, et al., Proc. Soc. Exp. Biol., 111, 544 (1962), whereby unanesthetized adult albino rats of 150-190 g. body weight are each numbered, weighed and marked with ink on the right lateral malleolus. One hour after administration of the drug by gavage, edema is introduced by injection of 0.05 ml. of 1% solution of carrageenin into the plantar tissue of the marked paws. Immediately thereafter, the volume of the injected paw is measured. The increase in volume three hours after the injection of carrageenin constitutes the individual response. Compounds are considered active if the difference in response between a control and the drug being tested is significant. Standard compounds are phenylbutazone at 33 mg./kg. and acetylsalicylic acid at 100 mg./kg., both with oral administration.

The tetracyclicimidazoles and the pharmaceutically acceptable salts thereof, which are useful antiinflammatory agents, may be administered either as individual therapeutic agents or as mixtures of therapeutic agents. They may be administered alone, but are generally administered with a pharmaceutical carrier selected on the basis of the chosen route of administration and standard pharmaceutical practice. For example, they may be administered orally in the form of tablets or capsules containing such excipients as starch, milk sugar or certain types of clay, etc. They may be administered orally in the form of elixirs or oral suspensions with the active ingredients combined with emulsifying and/or suspending agents. They may be injected parenterally, and

for this use they, or appropriate derivatives, may be prepared in the form of sterile aqueous solutions. Such aqueous solutions should be suitably buffered, if necessary, and should contain other solutes such as saline or glucose to render them isotonic.

Although the use of the present invention is directed toward the treatment of mammals in general, the preferred subject is humans. In determining an efficacious dose for human therapy, results of animal testing are frequently extrapolated and a correlation is assumed between animal test behavior and proposed human dosage. When a commercially employed standard is available, the dose level of the clinical candidate in humans is frequently determined by comparison of its performance with the standard in an animal test. For example, phenylbutazone is employed as a standard anti-inflammatory agent and is administered to humans at the rate of 100 to 400 mg. daily. It is assumed, then, that if compounds of the present invention have activity comparable to phenylbutazone in the test assay, that similar doses will provide comparable responses in humans.

Obviously, the physician will ultimately determine the dosage which will be most suitable for a particular individual, and it will vary with the age, weight and response of the particular patient as well as with the nature and extent of the symptoms and the pharmacodynamic characteristics of the particular agent to be administered. Generally, small doses will be administered initially, with a gradual increase in the dosage until the optimum level is determined. It will often be found that when the composition is administered orally, larger quantities of the active

ingredient will be required to produce the same level as produced by a small quantity administered parenterally.

Having full regard for the foregoing factors, an effective daily dosage of the compounds of the present invention in humans is approximately 0.1 to 1.0 g. per day, with a preferred range of about 0.2 to 0.8 g. per day in single or divided doses, or at about 3 to 10 mg./kg. of body weight will effectively alleviate inflammation in human subjects prone to said disorder. These values are illustrative, and there may, of course, be individual cases where higher or lower dose ranges are merited.

The following examples are provided solely for the purpose of illustration and are not to be construed as limitations of this invention, many variations of which are possible without departing from the spirit or scope thereof.

EXAMPLE I

8,9-Dihydro-2-(p-methoxyphenyl)dibenzo[3,4,7,8]cycloocta[1,2-d]imidazole (I: Z = $-CH_2CH_2-$; X, Y = H and R - p-$CH_3OC_6H_4$)

To a solution of 1.5 g. (6.4 m moles) of 11,12-dihydrocycloocta[a,e]dibenzene-5,6-dione in 50 ml. of dry glacial acetic acid contained in a three-necked flask and under a nitrogen atmosphere is added 3.0 g. of ammonium acetate. To the resulting dark yellow solution is added, dropwise, 1.1 g. (7.7 m moles) of p-methoxybenzaldehyde in 10 ml. of dry glacial acetic acid. The reaction mixture is heated to reflux overnight and is then cooled, poured into 300 ml. of ice - water and the pH adjusted to 7.0 by the addition of ammonium hydroxide solution. The resulting precipitate is filtered, dried and recrystallized from

benzene, 385 mg., m.p. 318-320° C. A second recrystallization from benzene provided the analytical sample, m.p. 321-323° C.

Anal. Calcd. for $C_{24}H_{20}N_2O$: C, 81.8; H, 5.7; N, 8.0.

Found: C, 81.2; H, 5.9; N, 7.6.

EXAMPLE II

Starting with 11,12-dihydrocycloöcta[a,e]dibenzene-5,6-dione and the requisite aldehyde, and repeating the procedure of Example I, the following compounds are prepared:

8,9-dihydro-2-phenyldibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 334-335° C.;

8,9-dihydro-2-(p-bromophenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 358-360° C.;

8,9-dihydro-2-(p-chlorophenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 347-348° C.;

8,9-dihydro-2-(3-pyridyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 285-286° C.;

8,9-dihydro-2-(p-methylthiophenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 329-331° C.;

8,9-dihydro-2-trifluoromethyldibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 290-292° C.;

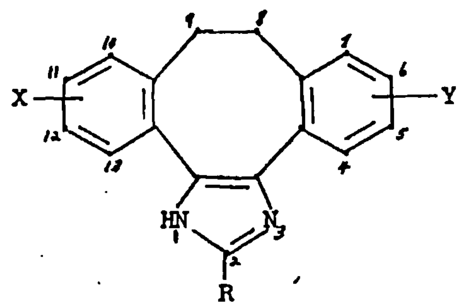
8,9-dihydro-2-(p-carboxyphenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 340-342° C.; and

8,9-dihydro-2-(p-dimethylaminophenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole, m.p. 308-311° C.

EXAMPLE III

The procedure of Example I is again repeated,

starting with the appropriately substituted α-diketone and aldehyde, to provide the following congeners:



X	Y	R	X	Y	R
H	H	$2\text{-}C_5H_4N$	H	$7\text{-}CH_3$	$\underline{m}\text{-}BrC_6H_4$
H	H	$4\text{-}C_5H_4N$	H	$7\text{-}CH_3$	$\underline{p}\text{-}CH_3SC_6H_4$
H	H	$\alpha\text{-}C_{10}H_7$	H	$7\text{-}CH_3$	$\underline{m}\text{-}CH_3SC_6H_4$
H	H	$\beta\text{-}C_{10}H_7$	H	$7\text{-}CH_3$	C_6H_5
H	H	$\underline{o}\text{-}CH_3C_6H_4$	H	$7\text{-}CH_3$	$\underline{m}\text{-}CH_3OC_6H_4$
H	H	$\underline{m}\text{-}CH_3C_6H_4$	H	$7\text{-}CH_3$	$\underline{o}\text{-}FC_6H_4$
H	H	$\underline{p}\text{-}CH_3C_6H_4$	H	$7\text{-}CH_3$	$\underline{p}\text{-}FC_6H_4$
H	H	$\underline{m}\text{-}CH_3OC_6H_4$	H	$4\text{-}CH_3O$	C_6H_5
H	H	$\underline{o}\text{-}FC_6H_4$	H	$4\text{-}CH_3O$	$\underline{p}\text{-}CH_3C_6H_4$
H	H	$\underline{p}\text{-}FC_6H_4$	H	$4\text{-}CH_3O$	$\underline{o}\text{-}CH_3OC_6H_4$
H	H	$\underline{m}\text{-}ClC_6H_4$	H	$4\text{-}CH_3O$	$\underline{p}\text{-}CH_3OC_6H_4$
H	H	$\underline{m}\text{-}Br_6C_4H$	H	$4\text{-}CH_3O$	$\underline{p}\text{-}HO_2CC_6H_4$
H	H	$\underline{o}\text{-}CH_3SC_6H_4$	H	$5\text{-}CH_3O$	C_6H_5
H	H	$\underline{m}\text{-}(CH_3)_2NC_6H_4$	H	$5\text{-}CH_3O$	$\underline{o}\text{-}CH_3C_6H_4$
H	$5\text{-}CH_3$	C_6H_5	H	$5\text{-}CH_3O$	$\underline{o}\text{-}FC_6H_4$
H	$5\text{-}CH_3$	CF_3	H	$5\text{-}CH_3O$	$\underline{m}\text{-}FC_6H_4$
H	$5\text{-}CH_3$	$\underline{p}\text{-}ClC_6H_4$	H	$5\text{-}CH_3O$	$\underline{m}\text{-}ClC_6H_4$
H	$5\text{-}CH_3$	$\underline{p}\text{-}CH_3C_6H_4$	H	$5\text{-}CH_3O$	$\underline{p}\text{-}ClC_6H_4$
H	$6\text{-}CH_3$	$3\text{-}C_5H_4N$	H	$5\text{-}CH_3O$	$\underline{p}\text{-}BrC_6H_4$
H	$6\text{-}CH_3$	$\underline{p}\text{-}CH_3OC_6H_4$	H	$5\text{-}CH_3O$	$\underline{p}\text{-}(CH_3)_2NC_6H_4$

X	Y	R	X	Y	R
H	6-CH_3	p-FC_6H_4	H	5-CH_3O	o-$CH_3SC_6H_4$
H	6-CH_3	m-FC_6H_4	H	5-CH_3O	CF_3
H	6-CH_3	p-$HO_2CC_6H_4$	H	6-CH_3O	C_6H_5
H	4-CH_3	3-C_5H_4N	H	6-CH_3O	p-$CH_3C_6H_4$
H	4-CH_3	p-$CH_3OC_6H_4$	H	6-CH_3O	o-$CH_3OC_6H_4$
H	4-CH_3	p-FC_6H_4	H	6-CH_3O	p-$CH_3OC_6H_4$
H	4-CH_3	m-FC_6H_4	H	6-CH_3O	p-$HO_2CC_6H_4$
H	4-CH_3	p-$HO_2CC_6H_4$	H	7-CH_3O	CF_3
H	7-CH_3	α-$C_{10}H_7$	H	7-CH_3O	o-FC_6H_4
H	7-CH_3	2-C_5H_4N	H	7-CH_3O	m-FC_6H_4
H	7-CH_3O	p-ClC_6H_4	H	7-CH_3O	β-$C_{10}H_7$
H	7-CH_3O	p-BrC_6H_4	H	4-Cl	CF_3
H	7-CH_3O	o-$CH_3SC_6H_4$	H	4-Cl	C_6H_5
H	7-CH_3O	3-C_5H_4N	H	4-Cl	p-$HO_2CC_6H_4$
H	7-CH_3O	o-$HO_2CC_6H_4$	H	4-Cl	p-$CH_3OC_6H_4$
H	4-F	CF_3	H	5-Cl	o-ClC_6H_4
H	4-F	p-$(CH_3)_2NC_6H_4$	H	5-Cl	m-ClC_6H_4
H	4-F	p-$CH_3C_6H_4$	H	5-Cl	o-FC_6H_4
H	4-F	m-$CH_3C_6H_4$	H	5-Cl	p-$CH_3OC_6H_4$
H	4-F	C_6H_5	H	5-Cl	p-$CH_3SC_6H_4$
H	5-F	C_6H_5	H	6-Cl	CF_3
H	5-F	CF_3	H	6-Cl	C_6H_5
H	5-F	3-C_5H_4N	H	6-Cl	p-$HO_2CC_6H_4$
H	5-F	o-$CH_3OC_6H_4$	H	6-Cl	p-$CH_3OC_6H_4$
H	5-F	p-$CH_3OC_6H_4$	H	7-Cl	CF_3
H	5-F	m-$CH_3OC_6H_4$	H	7-Cl	o-BrC_6H_4
H	5-F	p-BrC_6H_4	H	7-Cl	m-BrC_6H_4
H	5-F	p-ClC_6H_4	H	7-Cl	p-$HO_2CC_6H_4$
H	5-F	p-FC_6H_4	H	7-Cl	C_6H_5

X	Y	R	X	Y	R
H	6-F	CF_3	H	4-Br	CF_3
H	6-F	p-$(CH_3)_2NC_6H_4$	H	4-Br	C_6H_5
H	6-F	p-$CH_3C_6H_4$	H	4-Br	p-$CH_3CC_6H_4$
H	6-F	m-$CH_3C_6H_4$	H	5-Br	CF_3
H	6-F	C_6H_5	H	5-Br	o-$CH_3SC_6H_4$
H	7-F	α-$C_{10}H_7$	H	5-Br	o-$CH_3OC_6H_4$
H	7-F	β-$C_{10}H_7$	H	5-Br	p-$CH_3OC_6H_4$
H	7-F	C_6H_5	H	5-Br	p-$(CH_3)_2NC_6H_4$
H	7-F	m-$CH_3SC_6H_4$	H	5-Br	p-FC_6H_4
H	7-F	p-$CH_3OC_6H_4$	H	6-Br	CF_3
H	7-F	o-FC_6H_4	H	6-Br	C_6H_5
H	7-F	p-FC_6H_4	H	6-Br	p-$CH_3OC_6H_4$
H	7-Br	CF_3	H	6-CH_3S	p-$CH_3OC_6H_4$
H	7-Br	3-C_5H_4N	H	7-CH_3S	CF_3
H	7-Br	4-C_5H_4N	H	7-CH_3S	o-ClC_6H_4
H	7-Br	C_6H_5	H	7-CH_3S	p-ClC_6H_4
H	7-Br	p-ClC_6H_4	H	7-CH_3S	p-BrC_6H_4
H	4-CH_3S	CF_3	H	7-CH_3S	p-$CH_3C_6H_4$
H	4-CH_3S	α-$C_{10}H_7$	H	7-CH_3S	2-C_5H_4N
H	4-CH_3S	β-$C_{10}H_7$	H	7-CH_3S	3-C_5H_4N
H	4-CH_3S	p-$CH_3SC_6H_4$	H	7-CH_3S	4-C_5H_4N
H	4-CH_3S	p-$CH_3OC_6H_4$			
H	5-CH_3S	C_6H_5			
H	5-CH_3S	o-FC_6H_4			
H	5-CH_3S	m-FC_6H_4			
H	5-CH_3S	p-FC_6H_4			
H	5-CH_3S	m-$HO_2CC_6H_4$			
H	5-CH_3S	p-$(CH_3)_2NC_6H_4$			
H	6-CH_3S	CF_3			

X	Y	R
H	$6\text{-}CH_3S$	$\alpha\text{-}C_{10}H_7$
H	$6\text{-}CH_3S$	$\beta\text{-}C_{10}H_7$
H	$6\text{-}CH_3S$	$p\text{-}CH_3SC_6H_4$

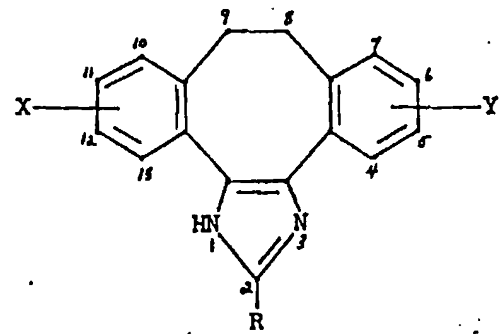
EXAMPLE IV

8,9-Dihydro-2-trifluoromethyl-5,12-dichlorodibenzo-[3,4,7,8]cycloöcta[1,2-d]imidazole (I: Z = $-CH_2CH_2-$; X, Y = Cl; R = CF_3)

A solution of 3.04 g. (10 m moles) of 11,12-dihydro-3,8-dichlorocycloöcta[a,e]dibenzene-5,6-dione in 100 ml. of anhydrous glacial acetic acid, under a nitrogen atmosphere, is treated with 4.7 g. of ammonium acetate followed by 4.3 g. (30 m moles) of trifluoroacetaldehyde ethyl hemiacetal in 50 ml. of the same solvent. The resulting solution is heated to reflux for 3 hours, an additional 4.3 g. of the hemiacetal added and heating continued for 3 hours more. The reaction mixture is cooled, poured into a mixture of ice and water and the pH adjusted to 7 using concentrated ammonium hydroxide solution. The crude product is filtered, dried and purified by recrystallization several times from toluene.

EXAMPLE V

Starting with the requisite 11,12-dihydrocycloöcta[a,e]dibenzene-5,6-dione and aldehyde, and following the procedure of Example IV, the following tetracyclic-imidazole analogs are synthesized:



X	Y	R	X	Y	R
13-CH_3	5-CH_3	CF_3	10-F	6-Cl	p-$CH_3C_6H_4$
13-CH_3	5-CH_3	p-$CH_3C_6H_4$	10-F	6-Cl	o-$CH_3C_6H_4$
13-CH_3	5-CH_3	p-$CH_3OC_6H_4$	10-F	6-Cl	α-$C_{10}H_7$
13-CH_3	5-CH_3	o-$CH_3OC_6H_4$	10-F	6-Cl	CF_3
13-CH_3	5-CH_3	p-FC_6H_4	13-Cl	6-Cl	CF_3
13-CH_3O	5-CH_3	m-FC_6H_4	13-Cl	6-Cl	3-C_5H_4N
13-CH_3O	5-CH_3	3-C_5H_4N	13-Cl	5-Br	o-$CH_3C_6H_4$
13-CH_3O	5-CH_3	4-C_5H_4N	13-Cl	5-Br	m-$CH_3C_6H_4$
13-CH_3O	5-CH_3	C_6H_5	13-Cl	5-Br	p-$CH_3C_6H_4$
13-CH_3O	7-CH_3	C_6H_5	11-Cl	5-Br	p-$CH_3OC_6H_4$
13-CH_3O	7-CH_3	CF_3	11-Cl	5-Br	CF_3
13-CH_3O	7-CH_3	p-$(CH_3)_2NC_6H_4$	11-Cl	5-CH_3O	CF_3
12-CH_3O	7-CH_3	p-$HO_2CC_6H_4$	11-Cl	5-CH_3O	C_6H_4
12-CH_3O	7-CH_3	α-$C_{10}H_7$	11-Cl	5-CH_3O	m-$CH_3SC_6H_4$
12-CH_3O	5-F	CF_3	11-Cl	5-CH_3O	p-$CH_3SC_6H_4$
12-CH_3O	5-F	C_6H_5	10-Br	5-CH_3O	p-$HO_2CC_6H_4$
11-CH_3O	5-F	2-C_5H_4N	10-Br	5-CH_3O	CF_3
11-CH_3O	5-F	4-C_5H_4N	10-Br	5-CH_3O	p-$(CH_3)_2NC_6H_4$
11-CH_3O	5-F	p-BrC_6H_4	10-Br	5-CH_3	p-$(CH_3)_2NC_6H_4$
11-CH_3O	6-F	p-$CH_3SC_6H_4$	10-Br	5-CH_3	CF_3
11-CH_3O	6-F	p-$CH_3OC_6H_4$	10-Br	5-CH_3	m-BrC_6H_4

X	Y	R	X	Y	R
12-CH_3O	6-F	*o*-FC_6H_4	10-Br	5-CH_3	*m*-ClC_6H_4
13-F	6-F	*o*-ClC_6H_4	13-CH_3S	5-CH_3	*p*-$CH_3SC_6H_4$
13-F	6-F	*p*-ClC_6H_4	13-CH_3S	5-CH_3	*m*-$CH_3SC_6H_4$
13-F	6-Cl	*p*-ClC_6H_4	13-CH_3S	5-CH_3	CF_3
13-F	6-Cl	*m*-ClC_6H_4	13-CH_3S	7-F	CF_3
13-F	6-Cl	*p*-$CH_3C_6H_4$	13-CH_3S	7-F	C_6H_5
11-F	6-Cl	β-$C_{10}H_7$	13-CH_3	7-F	β-$C_{10}H_7$
11-F	6-Cl	*o*-$(CH_3)_2NC_6H_4$	13-CH_3	7-F	3-C_5H_4N
11-F	6-Cl	*o*-$HO_2CC_6H_4$	13-CH_3	7-F	4-C_5H_4N
11-F	6-Cl	*m*-$CH_3OC_6H_4$	13-CH_3	7-F	*p*-BrC_6H_4
13-CH_3	5-Cl	*p*-ClC_6H_4	11-CH_3O	7-Br	*o*-BrC_6H_4
13-CH_3	5-Cl	*p*-FC_6H_4	11-CH_3O	7-Br	*p*-BrC_6H_4
13-CH_3	5-Cl	CF_3	11-CH_3O	7-Br	CF_3
13-CH_3	5-Cl	C_6H_5	11-CH_3O	5-CH_3S	CF_3
13-CH_3S	5-Cl	C_6H_5	11-CH_3O	5-CH_3S	C_6H_5
13-CH_3S	5-Cl	CF_3	11-CH_3O	5-CH_3S	*p*-ClC_6H_4
13-CH_3S	5-Cl	*p*-$(CH_3)_2NC_6H_4$	11-CH_3O	5-CH_3S	*p*-$CH_3OC_6H_4$
13-CH_3S	5-CH_3S	α-$C_{10}H_7$	11-CH_3O	7-CH_3O	*p*-$CH_3OC_6H_4$
13-CH_3S	5-CH_3S	β-$C_{10}H_7$	11-CH_3O	7-CH_3O	*m*-$CH_3C_6H_4$
13-CH_3S	5-CH_3S	CF_3	11-CH_3O	7-CH_3O	*o*-$CH_3C_6H_4$
10-Br	5-CH_3S	CF_3	11-CH_3O	7-CH_3O	*o*-$CH_3OC_6H_4$
10-Br	5-CH_3S	2-C_5H_4N	11-F	7-Br	*o*-FC_6H_4
10-Br	5-CH_3S	4-C_5H_4N	11-F	7-Br	*p*-FC_6H_4
10-Br	7-Br	C_6H_5			
10-Br	7-Br	*m*-$HO_2CC_6H_4$			
10-Br	7-Br	*p*-$HO_2CC_6H_4$			
11-F	7-Br	*p*-$CH_3SC_6H_4$			

EXAMPLE VI

2-Trifluoromethyldibenzo[b,f]thiepin[4,5-d]imidazole

(I: Z = S; X, Y = H and R = CF_3)

A mixture of 170 mg. (0.7 m mole) of 10,11-dihydrodibenzo/b,f/thiepin-10,11-dione, 300 mg. (2.1 m moles) of trifluoroacetaldehyde ethyl hemiacetal and 4.0 g. of ammonium acetate in 40 ml. of anhydrous glacial acetic acid is heated to the reflux temperature for one hour. An additional 170 mg. of diketone and 300 mg. of hemiacetal in 5 ml. of the same solvent are added and the refluxing continued for one more hour. The addition is repeated again, and the mixture heated at reflux temperatures for 3 hours. The reaction mixture is cooled, poured into ice - water and the pH adjusted with ammonium hydroxide to 7. The crude product is filtered, dried and recrystallized from benzene, 300 mg., m.p. 255-257° C.

Anal. Calcd. for $C_{16}H_9N_2SF_3$: C, 60.4; H, 2.8; N, 8.8.

Found: C, 60.4; H, 3.1; N, 8.6.

EXAMPLE VII

Starting with 10,11-dihydrodibenzo/b,f/thiepin-10,11-dione and the appropriate aldehyde and repeating the procedure of Example VI, the following compounds are prepared:

2-Phenyldibenzo/b,f/thiepin/4,5-d/imidazole, m.p. 312° C., dec.;

2-(p-methoxyphenyl)dibenzo/b,f/thiepin/4,5-d/imidazole, m.p. 300° C., dec.;

2-(p-bromophenyl)dibenzo/b,f/thiepin/4,5-d/imidazole, m.p. 334° C., dec.;

2-(p-chlorophenyl)dibenzo/b,f/thiepin/4,5-d/imidazole, m.p. 323° C., dec.;

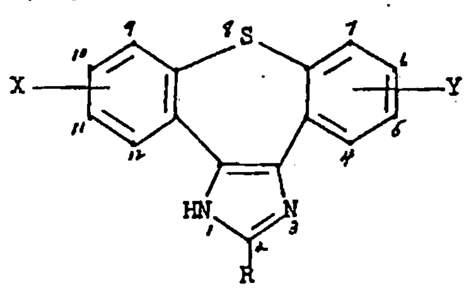
2-(3-pyridyl)dibenzo/b,f/thiepin/4,5-d/imidazole,

m.p. 230° C., dec.

2-(p-carboxyphenyl)dibenzo[b,f]thiepin[4,5-d]imidazole, m.p. 360° C.; and

2-(p-dimethylaminophenyl)dibenzo[b,f]thiepin[4,5-d]imidazole, m.p. 321° C., dec.

Starting with the appropriately substituted 10,11-dihydrodibenzo[b,f]thiepin-10,11-dione and requisite aldehyde, and employing the procedure of Example VI, the following compounds are prepared:



X	Y	R	X	Y	R
H	H	$-C_{10}H_7$	H	$5\text{-}CH_3O$	$2\text{-}C_5H_4N$
H	H	$-C_{10}H_7$	H	$5\text{-}CH_3O$	$4\text{-}C_5H_4N$
H	H	$2\text{-}C_5H_4N$	H	$5\text{-}CH_3O$	m-$CH_3C_6H_4$
H	H	p-FC_6H_4	H	$5\text{-}CH_3O$	p-$CH_3C_6H_4$
H	H	o-FC_6H_4	H	$5\text{-}CH_3O$	$-C_{10}H_7$
H	H	m-$HO_2CC_6H_4$	H	$7\text{-}CH_3O$	CF_3
H	H	o-$CH_3C_6H_4$	H	$7\text{-}CH_3O$	m-BrC_6H_4
H	H	o-$CH_3OC_6H_4$	H	$7\text{-}CH_3O$	p-BrC_6H_4
H	H	m-$CH_3OC_6H_4$	H	$7\text{-}CH_3O$	o-ClC_6H_4
H	H	p-$CH_3SC_6H_4$	H	$7\text{-}CH_3O$	o-FC_6H_4
H	$4\text{-}CH_3$	p-$CH_3SC_6H_4$	H	4-F	CF_3
H	$4\text{-}CH_3$	CF_3	H	4-F	C_6H_5
H	$4\text{-}CH_3$	C_6H_5	H	4-F	$3\text{-}C_5H_4N$
H	$4\text{-}CH_3$	p-$(CH_3)_2NC_6H_4$	H	4-F	$4\text{-}C_5H_4N$
H	$4\text{-}CH_3$	p-FC_6H_4	H	4-F	p-$CH_3SC_6H_4$

X	Y	R	X	Y	R
H	5-CH_3	p-FC_6H_4	H	6-F	CF_3
H	5-CH_3	p-ClC_6H_4	H	6-F	o-$CH_3OC_6H_4$
H	5-CH_3	p-BrC_6H_4	H	6-F	m-$CH_3OC_6H_4$
H	5-CH_3	o-$CH_3OC_6H_4$	H	6-F	p-$CH_3OC_6H_4$
H	5-CH_3	m-$CH_3C_6H_4$	H	6-F	p-$HO_2CC_6H_4$
H	7-CH_3	m-$HO_2CC_6H_4$	H	5-Cl	p-$HO_2CC_6H_4$
H	7-CH_3	p-$HO_2CC_6H_4$	H	5-Cl	α-$C_{10}H_7$
H	7-CH_3	p-$CH_3SC_6H_4$	H	5-Cl	β-$C_{10}H_7$
H	7-CH_3	α-$C_{10}H_7$	H	5-Cl	C_6H_5
H	5-CH_3O	CF_3	H	5-Cl	CF_3
H	5-CH_3O	C_6H_5	H	7-Cl	CF_3
H	7-Cl	o-FC_6H_4	H	5-CH_3S	α-$C_{10}H_7$
H	7-Cl	m-FC_6H_4	H	5-CH_3S	β-$C_{10}H_7$
H	7-Cl	p-FC_6H_4	H	5-CH_3S	3-C_5H_4N
H	7-Cl	p-$(CH_3)_2NC_6H_4$	H	5-CH_3S	4-C_5H_4N
H	7-Cl	m-$(CH_3)_2NC_6H_4$	H	5-CH_3S	CF_3
H	4-Br	o-$HO_2CC_6H_4$	H	5-CH_3S	o-$CH_3SC_6H_4$
H	4-Br	m-$HO_2CC_6H_4$	H	6-CH_3S	o-BrC_6H_4
H	4-Br	CF_3	H	6-CH_3S	m-BrC_6H_4
H	4-Br	C_6H_5	H	6-CH_3S	m-$(CH_3)_2NC_6H_4$
H	5-Br	C_6H_5	H	6-CH_3S	p-$HO_2CC_6H_4$
H	5-Br	p-$CH_3OC_6H_4$	H	7-CH_3S	p-$HO_2CC_6H_4$
H	5-Br	m-$CH_3OC_6H_4$	H	7-CH_3S	CF_3
H	5-Br	CF_3	H	7-CH_3S	C_6H_5
H	5-Br	p-$(CH_3)_2NC_6H_4$	H	7-CH_3S	o-ClC_6H_4
H	6-Br	p-$(CH_3)_2NC_6H_4$	H	7-CH_3S	p-ClC_6H_4
H	6-Br	CF_3	H	7-CH_3S	p-$CH_3C_6H_4$
H	6-Br	o-ClC_6H_4			
H	6-Br	p-ClC_6H_4			

X	Y	R	X	Y	R
H	5-CH_3S	p-FC_6H_4			
H	5-CH_3S	2-C_5H_4N			

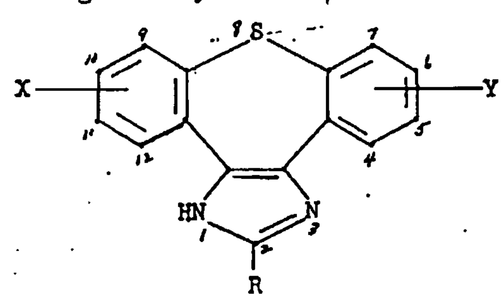
EXAMPLE IX

2-Phenyl-5,11-dichlorodibenzo[b,f]thiepin[4,5-d]imidazole (I: Z = S; X, Y = Cl; R = C_6H_5)

A mixture of 3.08 (0.01 mole) of 2,8-dichloro-10,11-dihydrobenzo[b,f]thiepin-10,11-dione, 7.0 g. of ammonium acetate and 1.28 g. (0.012 mole) of benzaldehyde in 85 ml. of dry glacial acetic acid is heated to reflux for 12 hours. The reaction mixture is cooled, poured into ice - water and ammonium hydroxide added until a pH of 7 is achieved. The precipitate is suction filtered and dried. Recrystallization from benzene provides the desired purified product.

EXAMPLE X

Employing the aforedexcribed procedure of Example IX, and starting with the requisite ketone and aldehyde, the following analogs are synthexized:



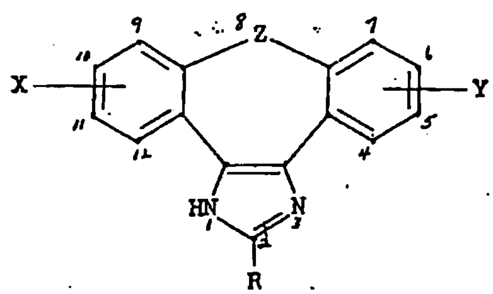
X	Y	R	X	Y	R
12-CH_3	4-CH_3	CF_3	12-Cl	4-Cl	p-ClC_6H_4
12-CH_3	4-CH_3	C_6H_5	12-Cl	4-Cl	p-FC_6H_4
12-CH_3	4-CH_3	3-C_5H_4N	12-Cl	4-Cl	o-BrC_6H_4
12-CH_3	4-CH_3	4-C_5H_4N	10-Cl	4-Cl	3-C_5H_4N
10-CH_3	4-CH_3	p-$HO_2CC_6H_4$	10-Cl	4-Cl	C_6H_5

X	Y	R	X	Y	R
10-CH_3	4-CH_3	p-$CH_3OC_6H_4$	10-Cl	5-Cl	C_6H_5
10-CH_3	5-CH_3	p-$CH_3OC_6H_4$	10-Cl	5-Cl	m-$HO_2CC_6H_4$
10-CH_3	5-CH_3	CF_3	10-Cl	5-Cl	p-$HO_2CC_6H_4$
10-CH_3	5-CH_3	p-$(CH_3)_2NC_6H_4$	10-Br	5-Cl	p-$(CH_3)_2NC_6H_4$
10-OCH_3	5-CH_3	α-$C_{10}H_7$	10-Br	5-Cl	m-BrC_6H_4
10-OCH_3	5-CH_3	β-$C_{10}H_7$	10-Br	5-Cl	CF_3
10-OCH_3	5-CH_3	p-$CH_3OC_6H_4$	10-Br	5-CH_3O	CF_3
10-OCH_3	5-F	m-$CH_3OC_6H_4$	10-Br	5-CH_3O	C_6H_5
10-OCH_3	5-F	m-$CH_3C_6H_4$	9-Br	5-CH_3O	m-FC_6H_4
10-OCH_3	5-F	o-FC_6H_4	9-Br	5-CH_3O	p-FC_6H_4
10-OCH_3	5-F	m-ClC_6H_4	9-Br	5-CH_3O	p-$CH_3SC_6H_4$
11-F	5-F	p-BrC_6H_4	9-Br	7-CH_3	CF_3
11-F	5-F	CF_3	9-Br	7-CH_3	o-$CH_3SC_6H_4$
11-F	5-CH_3O	CF_3	10-CH_3S	7-CH_3	3-C_5H_4N
11-F	5-CH_3O	C_6H_5	10-CH_3S	7-CH_3	4-C_5H_4N
11-F	5-CH_3O	p-FC_6H_4	10-CH_3S	7-CH_3	α-$C_{10}H_7$
11-F	5-CH_3O	o-$HO_2CC_6H_4$	10-CH_3S	5-Br	α-$C_{10}H_7$
11-F	5-CH_3O	o-$(CH_3)_2NC_6H_4$	10-CH_3S	5-Br	CF_3
9-F	5-CH_3O	2-C_5H_4N	10-CH_3S	5-Br	m-$CH_3OC_6H_4$
9-F	5-CH_3O	4-C_5H_4N	10-CH_3S	5-Br	o-$CH_3SC_6H_4$
9-F	7-CH_3O	m-$CH_3OC_6H_4$	9-F	5-Br	p-$CH_3C_6H_4$
9-F	7-CH_3O	p-$CH_3SC_6H_4$	9-F	5-Br	p-BrC_6H_4
9-F	7-CH_3O	p-BrC_6H_4	9-F	5-CH_3S	m-FC_6H_4
12-Cl	7-CH_3O	m-BrC_6H_4	9-F	5-CH_3S	p-FC_6H_4
12-Cl	7-CH_3O	β-$C_{10}H_7$	9-F	5-CH_3S	p-$HO_2CC_6H_4$
12-Cl	7-CH_3O	CF_3	9-F	5-CH_3S	p-$CH_3C_6H_4$
11-CH_3	5-F	CF_3	10-CH_3O	7-CH_3S	p-$CH_3OC_6H_4$
11-CH_3	5-F	C_6H_5	10-CH_3O	7-CH_3S	m-$CH_3SC_6H_4$
11-CH_3	5-F	p-$CH_3SC_6H_4$	10-CH_3O	7-CH_3S	p-$CH_3SC_6H_4$

X	Y	R	X	Y	R
11-CH_3	5-F	p-$CH_3OC_6H_4$	10-CH_3O	7-CH_3S	o-$HO_2CC_6H_4$
11-CH_3	5-Cl	CF_3	10-CH_3O	6-Br	p-$HO_2CC_6H_4$
11-CH_3	5-Cl	p-$(CH_3)_2NC_6H_4$	10-Br	6-Br	CF_3
11-CH_3	5-Cl	m-BrC_6H_4	10-Br	6-Br	o-$CH_3C_6H_4$
12-F	5-Cl	p-BrC_6H_4	10-Br	6-Br	m-$CH_3C_6H_4$
12-F	5-Cl	2-C_5H_4N	10-Br	6-Br	o-BrC_6H_4
12-F	5-Cl	3-C_5H_4N	10-Br	6-Br	m-ClC_6H_4
10-CH_3S	5-Cl	2-C_5H_4N			
10-CH_3S	5-Cl	CF_3			
10-CH_3S	5-Cl	C_6H_5			
10-CH_3S	7-CH_3S	C_6H_5			
10-CH_3S	7-CH_3S	CF_3			
10-CH_3S	7-CH_3S	p-FC_6H_4			

EXAMPLE XI

Employing the carrageenin rat foot edema test as a measure of anti-inflammatory activity, the following representative tetracyclicimidazoles were found to have the indicated activity at the specified dose:



X	Y	Z	R	Activity %Inhibition	Activity Dose mg./kg., P.O.
H	H	$-CH_2CH_2-$	C_6H_5	46	33
H	H	$-CH_2CH_2-$	p-ClC_6H_4	19	33
H	H	$-CH_2CH_2-$	3-C_5H_4N	21	33

X	Y	Z	R	Activity: % Inhibition	Activity: Dose mg./kg., P.O.
H	H	$-CH_2CH_2-$	p-$CH_3SC_6H_4$	20	33
H	H	$-CH_2CH_2-$	CF_3	20	33
H	H	$-CH_2CH_2-$	p-$HO_2CC_6H_4$	11	33
H	H	S	C_6H_5	19	33
H	H	S	p-$CH_3OC_6H_4$	35	33
H	H	S	p-BrC_6H_4	13	33
H	H	S	3-C_5H_4N	25	33
H	S	S	CF_3	36	33
H	S	S	CF_3	15	10
H	S	S	p-$HO_2CC_6H_4$	28	33
phenylbutazone				55	33

EXAMPLE XII

8.9-Dihydro-2-(p-methoxyphenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole hydrochloride

To a warm solution of 3.5 g. (0.01 mole) of 8,9-dihydro-2-(p-methoxyphenyl)dibenzo[3,4,7,8]cycloöcta[1,2-d]imidazole in 40 ml. of absolute methanol is added gaseous hydrogen chloride until the resulting precipitate of the hydrochloride salt ceases to form. The suspension is cooled in ice and the precipitate filtered and dried. An equal volume of diethyl ether is added to the filtrate, resulting in the precipitation of a second crop of the desired hydrochloride salt. The two fractions are combined and recrystallized from ethanol.

In an analogous manner, the compounds of the present invention are converted to their pharmaceutically acceptable acid addition salts.

EXAMPLE XIII

Suspension

A suspension of 2-phenyldibenzo/b,f7thiepein/4,5-d7-imidazole is prepared with the following composition:

Effective ingredient	100.00 g.
70% Aqueous sorbitol	741.29 g.
Glycerine, U.S.P.	185.35 g.
Gum acacia (10% solution)	100.00 ml.
Polyvinylpyrrolidone	0.50 g.
Distilled water	sufficient to make 1 liter

To this suspension, various sweeteners and flavorants are added to improve the palatability of the suspension. The suspension contains approximately 100 mg. of effective agent per milliliter.

EXAMPLE XIV

Solid Dispersion

A solid dispersion containing 20% 2-trifluoromethyl-dibenzo/b,f7thiepin/4,5-d7imidazole and 80% polyethylene glycol 6000 (PEG 6000) is prepared by adding in small portions and with constant stirring 100 g. of the imidazole to 500 g. of PEG 6000 heated to 70° C. When all the compound is added, the melt is "flash cooled" by cooling in an ice bath and the solidified product reduced to a fine powder and passed through a 100 mesh sieve. The material not passing through is recycled through the melting process.

EXAMPLE XV

Tablets

A tablet base is prepared by blending the following ingredients in the proportion by weight indicated:

Sucrose, U.S.P.	80.3

Tapioca starch	13.2
Magnesium stearate	6.5

Into this tablet base there is blended sufficient 2-trifluoromethyldibenzo/b,f7thiepin/4,5-d7imidazole to provide tablets containing 20, 100 and 250 mg. of active ingredient per tablet. The compositions are each compressed into tablets, each weighing 360 mg., by conventional means.

EXAMPLE XVI

Capsules

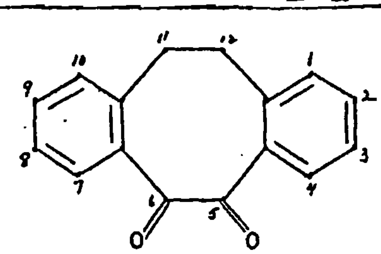
A blend is prepared containing the following ingredients:

Calcium carbonate, U.S.P.	17.6
Dicalcium phosphate	18.8
Magnesium trisilicate, U.S.P.	5.2
Lactose, U.S.P.	5.2
Potato starch	5.2
Magnesium stearate A	0.8
Magnesium stearate B	0.35

To this blend is added sufficient 8,9-dihydro-2- phenyldibenzo/3,4,7,87cycloocta/1,2-d7imidazole to provide capsules containing 50, 200 and 400 mg. of active ingredient per capsule. The compositions are filled into conventional hard gelatin capsules in the amount of 500 mg. per capsule.

Preparation A

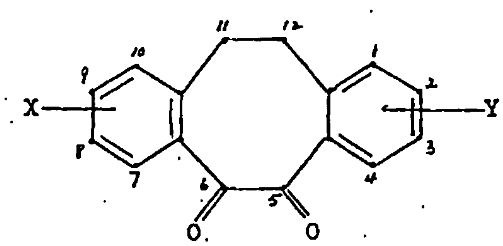
(a) 5,6,11,12-Tetrahydrodibenzo/a,e7cyclooctene-5,6-dione



To a suspension of 23.2 g. (0.209 mole) of selenium dioxide in 500 ml. of dry glacial acetic acid, under a nitrogen atmosphere and heated to 80° C., is added dropwise 42.0 g. (0.19 mole) of 5,6,11,12-tetrahydrobenzo[a,e]cyclooctene-5-one in 250 ml. of the same solvent. The reaction temperature is raised to 110° C. and maintained at this temperature for 5-6 hours. The mixture is cooled, poured slowly into 2500 ml. of ice - water and extracted several times with ethyl acetate. The organic layer is back-washed with a saturated sodium bicarbonate solution and dried over calcium sulfate. The calcium sulfate is filtered and the filtrate evaporated to dryness, leaving a yellow semi-solid, which on recrystallization from ethanol provided the desired product in three crystallization fractions, 3.8 g., 21.3 g. and 3.5 g., m.p.'s 130-132° C., 126-129° C. and 130-131° C., respectively. The three crops are combined and used without further purification.

Leonard, et al., J. Am. Chem. Soc., 77, 5078 (1955), reports a melting point of 131-132° C. for this material, prepared by a different method.

(b) The following 5,6,11,12-tetrahydrodibenzo[a,e]cyclooctene-5,6-diones, not previously reported in the chemical literature, are synthesized by the selenium dioxide oxidation of the corresponding monoketone:

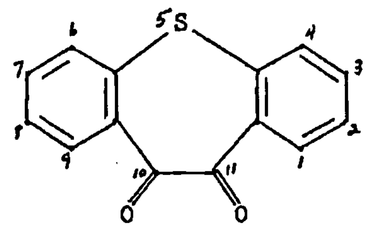


X	Y	X	Y
H	1-CH_3	7-CH_3	3-CH_3

X	Y	X	Y
H	2-CH_3	7-CH_3O	3-CH_3
H	3-CH_3	7-CH_3O	1-CH_3
H	4-CH_3	8-CH_3O	1-CH_3
H	1-CH_3O	8-CH_3O	3-F
H	2-CH_3O	9-CH_3O	3-F
H	3-CH_3O	9-CH_3O	2-F
H	4-CH_3O	8-CH_3O	2-F
H	1-F	7-F	2-F
H	2-F	7-F	2-Cl
H	3-F	9-F	2-Cl
H	4-F	10-F	2-Cl
H	1-Cl	7-Cl	2-Cl
H	2-Cl	7-Cl	3-Br
H	3-Cl	9-Cl	3-Br
H	4-Cl	9-Cl	3-CH_3O
H	1-Br	10-Br	3-CH_3O
H	2-Br	10-Br	3-CH_3
H	3-Br	7-CH_3S	3-CH_3
H	4-Br	7-CH_3S	1-F
H	1-CH_3S	7-CH_3	1-F
H	2-CH_3S	7-CH_3	3-Cl
H	3-CH_3S	7-CH_3S	3-Cl
H	4-CH_3S	7-CH_3S	3-CH_3S
10-Br	3-CH_3S	9-CH_3O	1-Br
10-Br	1-Br	9-CH_3O	3-CH_3S
9-F	1-Br	9-CH_3O	1-CH_3O

Preparation B

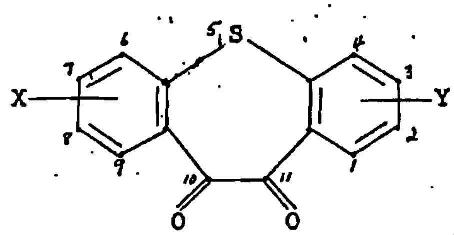
(a.) 10,11-Dihydrodibenzo/b,f7thiepin-10,11-dione



A mixture of 50 mg. (0.22 m mole) of 10,11-dihydrodibenzo/b,f/thiepin-10-one and 27 mg. (0.24 m mole) of selenium dioxide in 15 ml. of dry glacial acetic acid is heated at 80° C. until a solution is effected. The reaction temperature is then raised to 110° C. and maintained for 2 hours. The reaction mixture is filtered, poured into water and extracted with ethyl acetate. The organic layer is concentrated to dryness and the semi-solid triturated with hot benzene. Removal of the benzene provides the desired product as a yellow solid, 38 mg., m.p. 116-126° C. The analytical sample is triturated with diethyl ether, m.p. 120-126° C.

Anal. Calcd. for $C_{14}H_8O_2S$: C, 70.0; H, 3.3.
Found: C, 70.0; H, 3.5.

Following the above described oxidation procedure the following substituted 10,11-dihydrodibenzo/b,f/thiepin-10,11-diones, not previously known in the literature, are prepared:



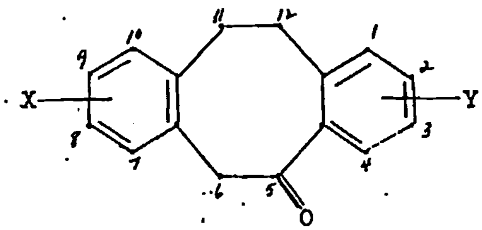
X	Y	X	Y
H	1-CH_3	6-F	2-CH_3O
H	2-CH_3	9-Cl	2-CH_3O

X	Y	X	Y
H	4-CH_3	9-Cl	1-Cl
H	2-CH_3O	7-Cl	1-Cl
H	4-CH_3O	7-Cl	2-Cl
H	1-F	7-Br	2-Cl
H	3-F	7-Br	2-CH_3O
H	2-Cl	6-Br	2-CH_3O
H	4-Cl	6-Br	4-CH_3
H	1-Br	7-CH_3S	4-CH_3
H	2-Br	7-CH_3S	2-Br
H	3-Br	6-F	2-Br
H	2-CH_3S	6-F	2-CH_3S
H	3-CH_3S	8-CH_3	2-F
H	4-CH_3S	8-CH_3	2-Cl
9-CH_3	1-CH_3	9-F	2-Cl
7-CH_3	1-CH_3	7-CH_3S	2-Cl
7-CH_3	2-CH_3	7-CH_3S	4-CH_3S
7-CH_3O	2-CH_3	7-CH_3O	4-CH_3S
7-CH_3O	2-F	7-CH_3O	3-Br
8-F	2-F	7-Br	3-Br
8-F	2-CH_3O		

Preparation C

11,12-Dihydrocycloöcta/a,e7dibenzen-5(6H)-ones

The following cycloöcta/a,e7dibenzen-5(6H)-ones, previously unreported in the chemical literature, are prepared according to the procedure as taught by Leonard, et al., J. Am. Chem. Soc., 77, 5078 (1955), and comprises cyclization of the appropriate 2-phenylethylphenylacetic acid with polyphosphoric acid at steam bath temperatures for 5-6 hours:



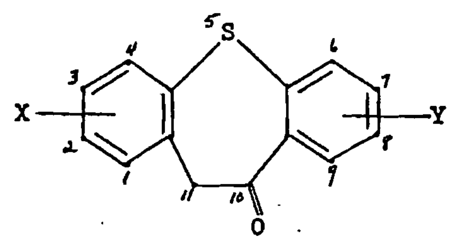
X	Y	X	Y
H	1-CH_3	H	1-Br
H	2-CH_3	H	2-Br
H	3-CH_3	H	3-Br
H	4-CH_3	H	4-Br
H	1-CH_3O	H	1-CH_3S
H	2-CH_3O	H	2-CH_3S
H	3-CH_3O	H	3-CH_3S
H	4-CH_3O	H	4-CH_3S
H	1-F	7-CH_3	3-CH_3
H	2-F	7-CH_3O	3-CH_3
H	3-F	7-CH_3O	1-CH_3
H	4-F	8-CH_3O	1-CH_3
H	1-Cl	8-CH_3O	3-F
H	2-Cl	9-CH_3O	3-F
H	3-Cl	9-CH_3O	2-F
H	4-Cl	8-CH_3O	2-F
7-F	2-F	9-Cl	3-CH_3O
7-F	2-Cl	10-Br	3-CH_3O
9-F	2-Cl	10-Br	3-CH_3
10-F	2-Cl	7-CH_3S	3-CH_3
7-Cl	2-Cl	7-CH_3S	1-F
7-Cl	3-Br	7-CH_3	1-F
9-Cl	3-Br	7-CH_3	3-Cl

X	Y	X	Y
7-CH_3S	3-CH_3S	7-CH_3S	3-Cl
10-Br	3-CH_3S	9-CH_3O	1-Br
10-Br	1-Br	9-CH_3O	3-CH_3S
9-F	1-Br	9-CH_3O	1-CH_3O

Preparation D

10,11-Dihydrodibenzo[b,f]thiepin-10-ones

Employing the procedure as taught by Jilek, *et al.*, *Monatsh. Chem.*, 96, 201 (1965, the following dibenzo[b,f]-thiepin-10-ones are prepared *via* cyclization of the requisite 2-phenylthiophenylacetic acid using polyphosphoric acid at 125° C. for 1-2 hours:



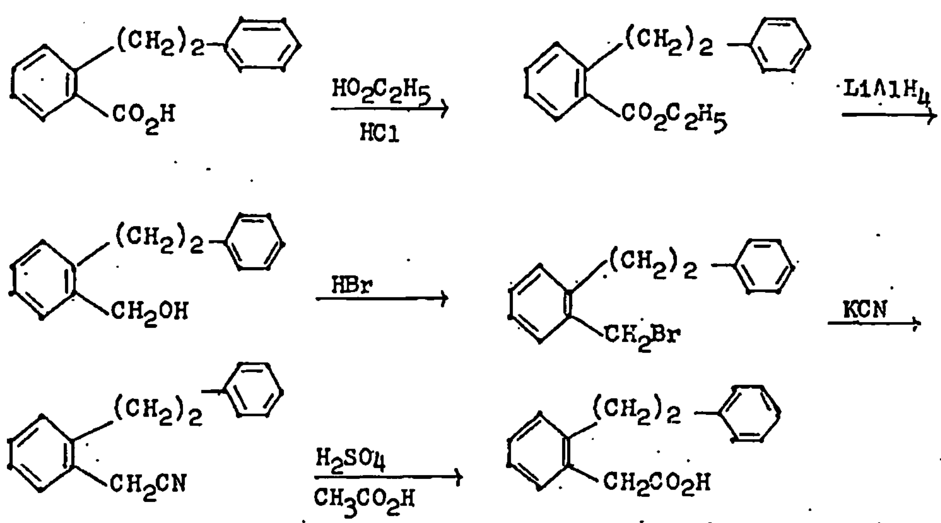
X	Y	X	Y
H	9-CH_3	4-F	8-CH_3
H	8-CH_3	1-Cl	8-CH_3
H	8-CH_3O	1-Cl	9-Cl
H	6-CH_3O	3-Cl	9-Cl
H	9-F	3-Cl	8-Cl
H	7-F	3-Br	8-Cl
3-Br	8-CH_3O	4-Br	8-CH_3O
H	9-Br	4-Br	6-CH_3
3-CH_3S	6-CH_3	3-CH_3S	8-Br
H	7-Br	4-F	8-Br
H	8-CH_3S	4-F	8-CH_3S
H	7-CH_3S	2-CH_3	8-F

X	Y	X	Y
H	6-CH_3S	2-CH_3	8-Cl
1-CH_3	9-CH_3	1-F	8-Cl
3-CH_3	9-CH_3	3-CH_3S	8-Cl
3-CH_3	8-CH_3	3-CH_3S	6-CH_3S
3-CH_3O	8-CH_3	3-CH_3O	6-CH_3S
3-CH_3O	8-F	3-CH_3O	7-Br
2-F	8-F	3-Br	7-Br
2-F	8-CH_3O		

Preparation E

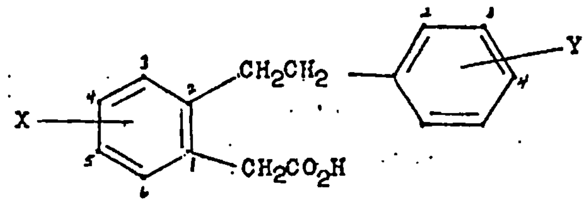
2-Phenylethylphenylacetic Acids

The above-mentioned 2-phenylethylphenylacetic acids are synthesized according to the sepuence of reactions as taught by leonard, *et al.*, *J. Am. Chem. Soc.*, 77, 5078 (1955), wherein, starting with 2-phenylethylbenzoic acid the following reactions are effected:



For convenience, the intermediate products are not purified or characterized, but used directly in the next step of the reaction sequence.

Employing the above-described reaction series, and starting with the requisite benzoic acid, the following, previously unreported 2-phenylethylphenylacetic acids, are prepared:



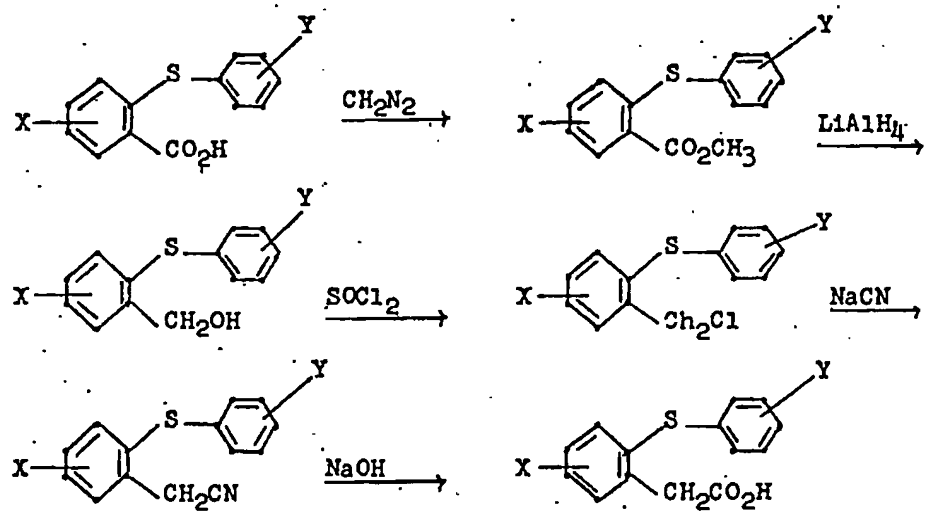
X	Y	X	Y
H	2-CH_3	H	2-CH_3S
H	3-CH_3	H	3-CH_3S
H	4-CH_3	H	4-CH_3S
H	2-CH_3O	6-CH_3	4-CH_3
H	3-CH_3O	6-CH_3O	4-CH_3
H	4-CH_3O	6-CH_3O	2-CH_3
H	2-F	5-CH_3O	2-CH_3
H	3-F	5-CH_3O	4-F
H	4-F	4-CH_3O	4-F
H	2-Cl	4-CH_3O	3-F
H	3-Cl	5-CH_3O	3-F
H	4-Cl	6-F	3-F
H	2-Br	6-F	3-Cl
H	3-Br	4-F	3-Cl
H	4-Br	2-F	3-Cl
6-Cl	3-Cl	6-CH_3	4-Cl
6-Cl	4-Br	6-CH_3S	4-Cl
4-Cl	4-Br	6-CH_3S	4-CH_3S
4-Cl	4-CH_3O	2-Br	4-CH_3S
2-Br	4-CH_3O	2-Br	2-Br
2-Br	4-CH_3	4-F	2-Br

X	Y	X	Y
6-CH_3S	4-CH_3	4-CH_3O	2-Br
6-CH_3S	2-F	4-CH_3O	4-CH_3S
6-CH_3	2-F	4-CH_3O	2-CH_3O

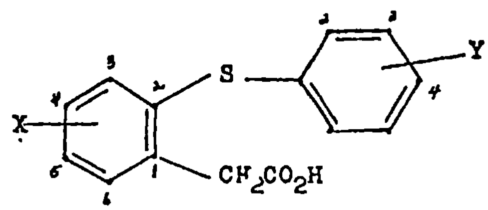
Preparation F

2-Phenylthiophenylacetic Acids

The requisite 2-phenylthiophenylacetic acids employed as intermediates leading to the products of the instant invention are prepared by the sequence of reactions as taught by Jilek, et al., Monatsh. Chem., 96, 201 (1965) and Protiva, et al., Csech. Patent 121,337 (C.A. 68, 105247t (1968) and comprises conversion of a 2-phenylthiobenzoic acid to the corresponding phenylacetic acid depicted below.



The intermediates are not purified or characterized, but are used directly in the next reaction. In the above-described manner, the following 2-phenylthiophenylacetic acids, not previously described in the chemical literature, are synthesized:

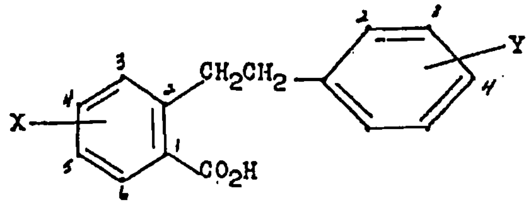


X	Y	X	Y
H	3-CH_3	3-F	4-CH_3O
H	4-CH_3	6-Cl	4-CH_3O
H	2-CH_3	6-Cl	3-Cl
H	4-CH_3O	4-Cl	3-Cl
H	2-CH_3O	4-Cl	4-Cl
H	3-F	4-Br	4-Cl
H	4-CH_3S	4-Br	4-CH_3O
3-Br	4-CH_3O	3-Br	2-CH_3
H	3-Br	4-CH_3S	2-CH_3
H	3-CH_3S	4-CH_3S	4-Br
H	2-CH_3S	3-F	4-Br
6-CH_3	3-CH_3	3-F	4-CH_3S
4-CH_3	3-CH_3	5-CH_3	4-F
4-CH_3	4-CH_3	5-CH_3	4-Cl
4-CH_3O	4-CH_3	6-F	4-Cl
4-CH_3O	4-F	4-CH_3S	4-Cl
5-F	4-F	4-CH_3S	2-CH_3S
5-F	4-CH_3O	4-CH_3O	2-CH_3S
4-CH_3O	3-Br	4-Er	3-Br

Preparation G

2-Phenylethylbenzoic Acids

The following 2-phenylethylbenzoic acids, not previously reported in the chemical literature, are prepared according to the procedure of Cope, et al., J. Am. Chem. Soc., 73, 1676 (1951) and comprises the red phosphorous - hydriodic acid reduction of the corresponding benzalphthalide:

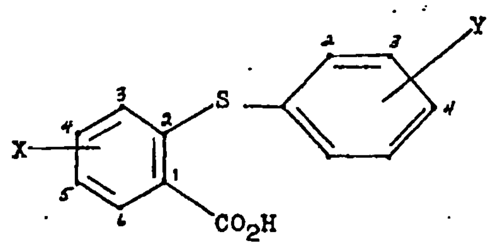


X	Y	X	Y
H	2-CH_3	H	2-CH_3
H	3-CH_3	H	3-CH_3S
H	4-CH_3	H	4-CH_3S
H	2-CH_3O	6-CH_3	4-CH_3
H	3-CH_3O	6-CH_3O	4-CH_3
H	4-CH_3O	6-CH_3O	2-CH_3
H	3-F	5-CH_3O	2-CH_3
H	4-F	5-CH_3O	4-F
H	2-Cl	4-CH_3O	4-F
H	3-Cl	4-CH_3O	3-F
H	4-Cl	5-CH_3O	3-F
H	2-Br	6-F	3-F
H	3-Br	6-F	3-Cl
H	4-Br	4-F	3-Cl
6-Cl	3-Cl	3-F	3-Cl
6-Cl	4-Br	6-CH_3S	2-F
4-Cl	4-Br	6-CH_3	2-F
6-CH_3S	4-CH_3S	6-CH_3	4-Cl
3-Br	4-CH_3S	6-CH_3	4-Cl
3-Br	2-Br	4-CH_3O	2-Br
4-F	2-Br	4-CH_3O	4-CH_3S
4-Cl	4-CH_3O	4-CH_3O	2-CH_3O
3-Br	4-CH_3O	3-Br	4-CH_3
6-CH_3S	4-CH_3		

Preparation H

2-Phenylthiobenzoic Acids

The following 2-phenylthiobenzoic acids, previously unreported in the chemical literature, are synthesized from the commercially available or known thiophenols and o-halobenzoic acids according to the method of Protiva, et al., Czech. Patent 121,337 (C.A. 68, 105247t; 1968) and Mahishi, et al., J. Karnatak Univ., 2, 50 (1957) (C.A., 53, 14101h; 1959).



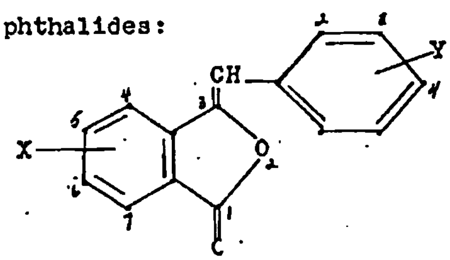
X	Y	X	Y
H	3-CH_3	3-F	4-CH_3O
H	4-CH_3	6-Cl	4-CH_3O
H	2-CH_3	6-Cl	3-Cl
H	4-CH_3O	4-Cl	3-Cl
H	2-CH_3O	4-Cl	4-Cl
H	3-F	4-Br	4-Cl
4-Br	4-CH_3O	3-Br	4-CH_3O
H	3-Br	3-Br	2-CH_3
H	4-CH_3S	4-CH_3S	2-CH_3
H	3-CH_3S	4-CH_3S	4-Br
H	2-CH_3S	3-F	4-Br
6-CH_3	3-CH_3	3-F	4-CH_3S
4-CH_3	3-CH_3	5-CH_3	4-F
4-CH_3	4-CH_3	5-CH_3	4-Cl

X	Y	X	Y
4-CH_3O	4-CH_3	6-F	4-Cl
4-CH_3O	4-F	4-CH_3S	4-Cl
5-F	4-F	4-CH_3S	2-CH_3S
5-F	4-CH_3O	4-CH_3O	2-CH_3S
4-CH_3O	3-Br	3-Br	3-Br

Preparation I

Benzalphthalides

Employing the procedures of Weiss, "Organic Syntheses," Coll. Vol. 2, John Wiley & Sons, Inc., New York, N. Y., 1948, page 61, Hrnciar, *et al*., *Chem. Zvesti*., **21**, 267 (1967) (*C.A.* **67**, 73304v; 1967) and Hrnciar, *ibid*., **16**, 96 (1962) (*C.A.* **59**, 2731; 1963), the following benzalphthalides, not previously reported in the literature, are synthesized either *via* the condensation of the commercially available or known phenylacetic acids and phthalic anhydrides or benzaldehydes and phthalides:

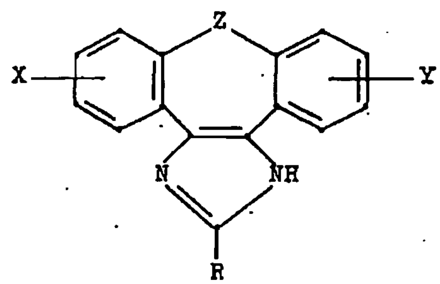


X	Y	X	Y
H	2-CH_3S	H	3-CH_3S
7-CH_3	4-CH_3	7-Cl	3-Cl
7-CH_3O	4-CH_3	7-Cl	4-Br
7-CH_3O	2-CH_3	5-Cl	4-Br
6-CH_3O	2-CH_3	7-CH_3S	4-CH_3S
6-CH_3O	4-F	4-Br	4-CH_3S
5-CH_3O	4-F	4-Br	2-Br
5-CH_3O	3-F	5-F	2-Br

X	Y	X	Y
6-CH_3O	3-F	5-Cl	4-CH_3O
7-F	3-F	4-Br	4-CH_3O
7-F	3-Cl	4-Br	4-CH_3
5-F	3-Cl	7-CH_3S	4-CH_3
4-F	3-Cl	7-CH_3S	2-F
7-CH_3	2-F	7-CH_3	4-Cl
7-CH_3S	4-Cl	5-CH_3O	2-Br
5-CH_3O	4-CH_3S	5-CH_3O	2-CH_3O

The embodiments of the invention in which an exclusive property or privilege is claimed are defined as follows:

1. A process of preparing a compound selected from those of the formula:



...I

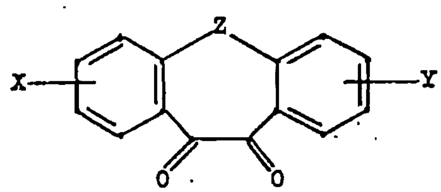
and the pharmaceutically acceptable acid addition salts thereof wherein:

Z is ethylene or sulphur;

X and Y are each the same or different and are hydrogen, methyl, methoxy, fluorine, chlorine, bromine, or methylthio; and

R is trifluoromethyl, pyridyl, naphthyl or phenyl and substituted phenyl wherein said substituent is methyl, methoxy, fluorine, chlorine, bromine, dimethylamino, carboxy or methylthio,

characterized by reacting a diketone of the formula:



wherein X, Y and Z are as defined above,

with an aldehyde of the formula:

RCHO

wherein R is as defined above,

and ammonium acetate,

and, if desired, preparing the pharmaceutically acceptable salts thereof.

2. Compounds of the Formula I as defined in claim 1, whenever prepared by the process of claim 1 or by an obvious chemical equivalent thereof.